Quantification of the drug effect and exploration of mechanism of action of two NMDA channel blockers, AZD6765 and ketamine, using mouse EEG

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Introduction

AZD6765, an NMDA channel blocker and ketamine, an NMDA antagonist differ in how they interact with the NMDA channel. AZD6765 is a low-trapping whereas ketamine is a high-trapping compound. Ketamine has shown effects in major depressive disorder (MDD) [1] and AZD6765 is under clinical development for treatment of MDD. A therapeutic hypothesis is that NMDA channel blockers normalize electrical activity in depression-associated brain networks. Change in the EEG amplitude within the γ frequency band (35 to 55 Hz) is a potential pharmacodynamic (PD) biomarker of these compounds.

Objectives

The primary objective was to estimate the potency and efficacy of AZD6765 and ketamine, using the change in γEEG.

The secondary objective was to explore the biomarker hypothesis (Fig 1) that the degree of trapping in the NMDA ion channel affects the underlying mechanism of action on the γEEG.

Fig 1. Biomarker hypothesis

Methods

The pharmacokinetics (PK) and PK-PD were analyzed using NONMEM 7.1.2 with the optimization routine FOCE INTERACTION. Models were selected based on the objective function value and/or diagnostic plots.

The PK of the compounds was obtained from satellite animals and estimated typical population PK parameters were used as input for the analysis of the EEG exposure-response relationship of the compounds.

The EEG was recorded, in 2 min bins, in male C57BL6 mice. Following a 30 min baseline recording mice were administered AZD6765, ketamine or vehicle ip and the EEG recording continued for 90 min post-dose. The doses of AZD6765 were 18, 74, 111, 222 and 370 µmol/kg and of ketamine 55, 109, 219, 438, and 547 µmol/kg.

Results

Both AZD6765 and ketamine increased the γEEG with increasing plasma concentration (Figs 2 and 3). For AZD6765, the delay between the change in plasma concentration and γEEG was best described with a turnover model with inhibition of the turnover rate, using a sigmoidal E_{max} model (Table 1 and 2). In addition, a negative feedback mechanism (tolerance) [2] was identified. The ketamine data could not be described assuming an inhibition of the turnover rate, but were best described using a combination of a direct and a delayed effect. The delay was described using a turnover model with stimulation of the production of the EEG signal (Table 1 and 2).

Table 1. Final models

	Conc-eff	Indirect response	Negative feedback
AZD6765	Sigm E_{max}	Inhibition K_{out} DADT(R) = K_{in}-K_{out}*(1-EFF)*A(M)	DADT(M) = K_{tol}*A(R)-K_{tol}*A(M)
Ketamine	*2 effects* Direct: Linear Indirect: Sigm E_{max}	Stimulation K_{in} DADT(R)=K_{in}*(1+EFF)-K_{out}*R	NA

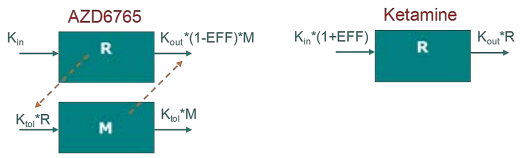
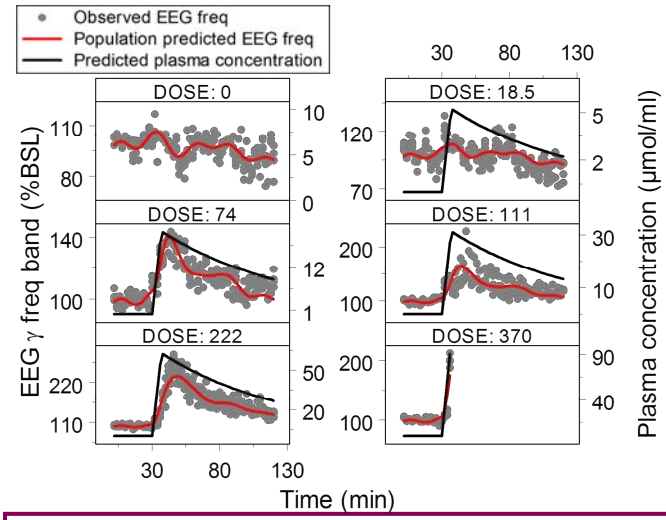


Table 2. Final parameters

	EC_{50} (µM)	E_{max}	Hill	K_{out} (1/min)	Slope (µM)	K_{tol}	ETA EC_{50}	Res error
AZD6765	49.4 (44.6-54.2)	1 FIX	1.27 (1.2-1.3)	0.307 (0.29-0.33)	NA	0.146 (0.14-0.16)	0.0201 (0.0042-0.036)	0.00492 (0.003-0.006)
Ketamine	17 (12.7-21.3)	3.37 (0.1-5.8)	8.31 (3.7-12.9)	0.014 (0.001-0.03)	2.63 (2.1-3.6)	NA	0.138 (-0.09-0.4)	0.014 (0.01-0.02)

Fig 2. AZD6765 plasma concentration and EEG data vs time

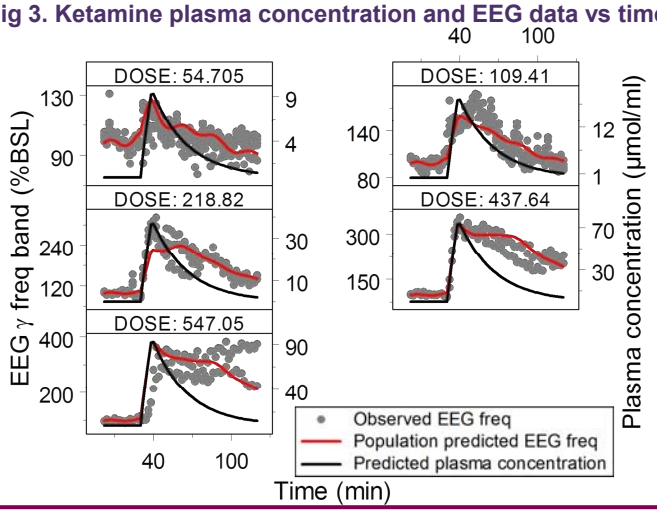


AZD6765

A small delay between the increase in plasma concentration (CP) and the increase in γEEG

The γEEG response decreases faster than the CP indicating a negative feed-back mechanism

Fig 3. Ketamine plasma concentration and EEG data vs time



Ketamine

No delay between the increase in CP and the increase in γEEG but with increasing doses the EEG response is delayed indicating two different effects

Discussion and Conclusions

- Both AZD6765 and ketamine increased γEEG
- PK-PD modelling of the γEEG supported the biomarker hypothesis that the degree of trapping in the NMDA channels affects the mechanism by which changes in γEEG are induced
- The effect of AZD6765, a low-trapping compound, was best described by an inhibition of K_{out}
- In contrast, the effect of ketamine, a high-trapping compound, could not be described by an inhibition of K_{out}, but were best described using a combination of a direct effect and a delayed increase in K_{in}

References

[1] Zarate CA, et al. *Arch Gen Psychiatry*. 2006;63:856-864.

[2] Gabrielsson J, Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis, 4th edition.

Disclosures

C Wallsten, M Quirk, C Fonck, and B Ploeger are employees and P Ekerot is a former employee of AstraZeneca R&D. O Ackaert and N Snelder are employees of LAP&P.

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